November 22, 2002

Elmer Rauckman, Ph.D., DABT
Consulting Toxicologist
1201 Anise Court
Freeburg, IL 62243

(For BASF Corporation)

Dear Dr. Rauckman:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Dicamba and Acifluorfen Intermediates Category posted on the ChemRTK HPV Challenge Program Web site on January 31, 2002. I commend BASF Corporation for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that BASF Corporation advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Dicamba and Acifluorfen Intermediates Category

SUMMARY OF EPA COMMENTS

The sponsor, BASF Corporation, submitted a test plan and robust summaries to EPA for the Dicamba and Acifluorfen Intermediates Category dated December 20, 2001. EPA posted the submission on the ChemRTK HPV Challenge Website on January 31, 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category into three subgroups is acceptable, except that for ecological effects structural dissimilarity within one subgroup (Group II) requires testing more than one representative substance.

2. Physicochemical Properties. (a) The submitter needs to provide measured melting point data for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid and for one representative salt for each category. (b) EPA agrees with the submitter's approach to boiling point and vapor pressure except that measured values are needed for 2,5-dichloroanisole. (c) EPA agrees with the submitter's approach to partition coefficient and water solubility except that measured values are needed for 2,5-dichloroanisole, 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid, and 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid potassium salt.

3. Environmental Fate. EPA generally agrees with the submitter's approach. The submitter needs to provide measured biodegradation data for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid or its potassium salt. The submitter needs to specify the OECD Guideline it plans to use.

4. Health Effects. (a) Data needs for Groups I and III are met by the combination of submitted data and the read-across strategy. (b) For Group II the proposed combined repeated-dose and reproductive/ developmental toxicity testing on 2,5-dichloroanisole is sufficient to satisfy the health effects endpoints. (c) The submitter needs to address deficiencies in the robust summaries.

5. Ecological Effects. (a) Adequate data are available for Group I . (b) EPA agrees that testing of all endpoints is necessary for Group II. The submitter did not supply a rationale for testing only 2,5-dichloroanisole. EPA believes that testing of that substance and an additional Group II member is needed. (c) Existing Group III data are adequate for fish and invertebrates; inadequate data were submitted for algae. The submitter needs to provide an algae study for a category chemical or an appropriate analog.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON DICAMBA AND ACIFLUORFEN INTERMEDIATES CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposed a category of nine sponsored substances that are intermediates in the production of dicamba and acifluorfen. The submitter also included dicamba, acifluorfen, and acifluorfen sodium salt as analogs to provide supporting data for the category. The submitter subdivided the category into three groups:

Group I members are dicamba sodium salt (CAS No. 1982-69-0), 3,6-dichloro-2-hydroxybenzoic acid, potassium sodium salt (CAS No. 68938-79-4), and 3,6-dichloro-2-hydroxybenzoic acid, dipotassium salt (CAS No. 68938-80-7). Supporting analog: dicamba (3,6-dichloro-2-methoxybenzoic acid, CAS No. 1918-00-9).

Group II members are 2,5-dichlorophenol (CAS No. 583-78-8), its sodium (CAS No. 52166-72-0) and potassium (CAS No. 68938-81-8) salts and the O-methyl derivative, 2,5-dichloroanisole (CAS No. 1984-

58-3). Group II members lack the carboxylic acid function present in Group I.

Group III members are two acifluorfen intermediates, 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid (CAS No. 63734-62-3) and 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid, potassium salt (CAS No. 72252-48-3). Supporting analogs are acifluorfen (6-nitro-3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid (CAS No. 50594-66-6), and its sodium salt (6-nitro-3-(2-chloro-4-(trifluoro-methyl)phenoxy)benzoic acid, sodium salt (CAS No. 62476-59-9). Acifluorfen and its salt contain an aromatic nitro function not present in the two Group III members.

The category definition is clear and specific.

Category Justification

Because there are large structural variations among the category members, the submitter subdivided the members into three groups, each based on a common structure. The submitter justifies the subdivision on the basis of structure and the expectation that the members of each group will have similar environmental and toxicological properties. The data provided by the submitter generally support the groups from the standpoint of the physicochemical and environmental fate properties of the members. However, some additional information is needed to support the comparison of aquatic and of mammalian toxicological effects among compounds within a group to support the submitter's postulated pattern of similar toxicities.

Health effects. The submitter justified grouping acid and salt forms of compounds based partly on the basis of toxicokinetic data for dicamba free acid and three amine salts (test plan pp. 3, 5). This is reasonable, but the submitter needs to identify the salts.

The submitter supported the category on the basis of similar acute oral LD50 values (1352-1870 mg/kg) for dicamba and its salts (Group I). This argument also pertains to the reported acute oral toxicity values for members of the other two groups: 2475 mg/kg for 2,5-dichlorophenol (Group II) and 1170 or 1540 mg/kg for two Group III compounds.

EPA agrees that the inclusion of 2,5-dichloroanisole in Group II (the only member without an ionizable group) is justified on the basis of its expected O-demethylation to 2,5-dichlorophenol in animals.

Ecotoxicity. For Groups I and III, all members are structurally similar and have ionizable groups. Extrapolating experimental aquatic toxicity data available for at least one of the members in each group to the other members of the group is reasonable. In the case of Group II, the dissimilarity in structure between the methoxy- and hydroxybenzene systems argues against extrapolating between them.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

Melting point. The estimated data for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid (Group III) and for the category salts are inadequate. The submitter needs to provide measured melting point (decomposition) data for the benzoic acid derivative and for one representative salt from each subcategory. As a rule, measured physicochemical property data should be supplied, both to characterize a substance and to provide inputs to transport/distribution models, unless precluded by experimental obstacles. The use of estimated or calculated values introduces uncertainties that then become magnified in modeling applications. Data from standard reference works are acceptable, as long as the submitter identifies the original source.

Boiling Point. EPA agrees with the submitter that measured boiling points are not needed for the salts in the category. The submitted data for 2,5-dichlorophenol in the Group 2 subcategory are adequate. The submitter needs to supply measured boiling (decomposition) point data for 2,5-dichloroanisole. As indicated above, estimated data may create uncertainty in modeling applications..

Vapor Pressure. EPA agrees with the submitter that measured vapor pressures are not needed for the salts in the category. The submitter needs to provide measured vapor pressure data for 2,5-dichloroanisole.

In Table 4.2 of the test plan (page 24), the submitter indicates that 2,5-dichlorophenol has a calculated (EPIWIN) vapor pressure of 0.61 hPa. However, its robust summary reports a literature value of 0.08 hPa, supported by an EPIWIN value of 0.06 hPa. The submitter needs to address this discrepancy.

Partition Coefficient. EPA agrees with the submitter's reasoning for not further testing the partition coefficient of the salts listed in all three subcategories except for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid, potassium salt, listed under the Group III subcategory. According to OECD Guideline 107, this value should be measured by "Partition Coefficient (n-octanol/water), Flask-shaking Method." In addition, a recent workshop to evaluate changes in OECD Guidelines to account for measuring the log K_{ow} of ionizable compounds was held in November 2000 (OECD 2000). In general, the "real" log K_{ow} should be reported for the neutral species which must be measured at the appropriate pH (preferably one pH unit below the pK_a value) and the "apparent" log K_{ow} (sometimes referred to as logD) can be measured or estimated at various pH values. The submitted value for the supporting chemical (acifluorfen sodium salt) ranged from 0.049 to 1.19, and using this value to validate the submitted estimated value is inadequate. A measured value should be obtained for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid, potassium salt. For dicamba, EPA suggests using the value of 2.21 at 25°C which is the log K_{ow} for the neutral species.

Measured values should also be obtained for 2,5-dichloroanisole in Group II and 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid in Group III. Estimated values for these substances appear out of line with values supplies for other members.

Water Solubility. EPA agrees that measured water solubilities are not needed for the salts in the category except for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid, potassium salt, (Group 3). Because the estimated value for this substance did not compare as expected with the measured values for the other supporting chemicals in its group (acifluorfen and acifluorfen sodium salt), the submitter needs to provide measured water solubility data for this chemical.

The submitted data for 2,5-dichloroanisole in the Group II subcategory and 3-(2-chloro-4-(trifluoromethyl)-phenoxy)benzoic acid in the Group 3 subcategory are estimated values and are inadequate. The submitter needs to provide measured water solubility data for both substances.

<u>Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)</u>

EPA agrees with the submitter's approach to photodegradation, stability in water and fugacity.

Biodegradation. EPA agrees with the submitter's proposal to provide biodegradation data for dicamba and 2,5-dichloroanisole. The submitter also proposed testing of acifluorfen, sodium salt. However, considering that this salt is not a sponsored category member and also has a nitro group, it is more appropriate for the submitter to provide measured biodegradation data for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid or its potassium salt in order to have a more accurate picture of the biodegradation of the HPV chemicals in group III. The submitter needs to specify the OECD Guideline it plans to use.

The submitter concluded that it cannot be determined if 2,5-dichlorophenol is considered readily biodegradable by OECD criteria, but did not recommend further testing of 2,5-dichlorophenol or its salts in the test plan. However, EPA located data for the biodegradation of 2,5-dichlorophenol using OECD method 301C and the Japanese MITI test (JAPAN 1992) that appear to satisfy the endpoint for this substance. The submitter needs to include this information in the test plan and summaries.

<u>Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).</u>

For the purposes of the HPV Challenge program, all health effects endpoints for Groups I and III are satisfied by the combination of submitted data and the read-across strategy. The proposed testing of 2,5-dichloroanisole is sufficient to satisfy the health effects endpoints for Group II.

Although the test plan states that there are mammalian toxicity data for 2,5-dichloroanisole (p. 14), no robust summaries were submitted and the data are not reflected in Tables 4 or 4.2. These data, if available, need to be summarized and submitted to EPA. If data are not available, the statement on page 14 needs to be revised.

Group III. 3-(2-Chloro-4-(trifluoromethyl)phenoxy)benzoic acid. The submitter incorrectly rated the first oral study (which reported an LD50 of 1170 mg/kg) as invalid, because the density of the oil was not reported. However, despite the difficulty in obtaining results based on the active ingredient, EPA considers the study to be adequate.

Ecotoxicity

The submitter proposed no additional testing for Group I or Group III chemicals. Testing was proposed for acute studies of the Group II chemical 2,5-dichloroanisole in fish, daphnia, and algae.

Group I. EPA located studies not provided by the submitter of fish, invertebrates, and algae in the EFED Pesticide Database (EFED 2000) for the Group I supporting chemical dicamba and a sponsored chemical, dicamba sodium salt. The studies of dicamba in daphnia and of dicamba sodium salt in green algae are adequate. The combination of data in the EFED Pesticide Database and the submitted robust summaries are adequate to address the ecotoxicity endpoints for Group I.

Group II. While the submitter did not supply a rationale for testing only 2,5-dichloroanisole, EPA agrees with the submitter's proposal to conduct acute testing in fish, invertebrates, and algae for the Group II chemical 2,5-dichloroanisole using OECD Guidelines 203, 202, and 201, respectively. The tests should be performed up to the water solubility limit, estimated in the test plan as 75 mg/L. Because the remaining three chemicals in Group II differ from 2,5-dichloroanisole in that each is a phenol or phenol salt, EPA believes aquatic data should be supplied on one of these chemicals. EPA has located an adequate study on 2,5-dichlorophenol in the freshwater fish species *Oryzias latipes* in the ECOTOX database (2002) that appears to satisfy the fish endpoint for the ionizable group members.

Group III. The submitter proposed no testing. Although the existing data are adequate for fish and invertebrates, inadequate data were submitted for algae species *Selenastrum* and *Skeletonema.* The submitter needs to provide a 72-hour or 96-hour definitive EC50 value in algae for these tests or for another Group III chemical. All other tested aquatic plant species were inappropriate.

Fish. Adequate data exist for the Group III chemicals in fish from studies submitted for 3-(2-chloro-4-(trifluoromethyl)phenoxy)benzoic acid and the analog acifluorfen sodium salt.

Invertebrates. The study of acifluorfen sodium salt is adequate for the purposes of the HPV Challenge Program. A minor discrepancy in reporting of this EC50 in the test plan (p. 25) and IUCLID summary (p. 15), and as an LC50 elsewhere in the test plan (p18) needs to be corrected.

Specific Comments on the Robust Summaries

Health Effects

EPA reviewed 22 unique robust summaries for health effects studies: *Group I* - six for dicamba, one for sodium dicamba, and one (submitted twice) for 3,6-dichloro-2-hydroxybenzoic acid as an analog to its sodium potassium and dipotassium salts; *Group II* - four for 2,5-dichlorophenol; *Group III* - one for acifluorfen, two (one duplicated) for 3-(2-chloro-4-trifluoromethyl)phenoxybenzoic acid, and seven for sodium acifluorfen. The quality of these studies was generally good; although many studies predated GLP guidelines, nearly all followed EPA or OECD guidelines or equivalent methods.

In some studies, it was unclear whether the test material was a simple technical grade solution or a formulated herbicide containing a high proportion (60 to 80%) of undefined ingredients. The submitter needs to identify such ingredients and discuss their known or suspected influence on the test results.

In the following comments, each chemical name is preceded by its Group number.

Acute Toxicity.

Group II. 2,5-Dichlorophenol. The robust summary did not report test substance purity or dose volume.

Group III. Sodium acifluorfen. The study differed from OECD Guideline 401 because only males were examined, but the group size (10/dose) was adequate.

Repeated-Dose Toxicity.

Group II. 2,5-Dichlorophenol. The robust summary for a 4-week inhalation bioassay in rats omitted the method of generating the test atmosphere. The original study was similar to OECD guideline 407, but did not evaluate blood clotting parameters and did not report test substance purity.

Group III. Sodium acifluorfen. The robust summary for a guideline-like 90-day bioassay in rats dietarily exposed to Tackle 2AS (~20-21% a.i.) did not report the size of changes in body and organ weights or specify the 'liver damage' observed in high-dose rats. The study differed from OECD Guideline 408 because it did not examine target organs (liver and kidney) in mid- and low-dose rats for histopathology.

Genetic Toxicity.

Group I. Dicamba. The robust summary for a negative GLP-compliant *in vitro* chromosomal aberration assay provided sufficient information to evaluate the study but omitted some methodological details (culture harvest time and use of colcemid).

Group III. 3-(2-Chloro-4-(trifluoromethyl)phenoxy)benzoic acid. Two identical robust summaries were submitted for a negative guideline-like assay for mutation in bacteria.

Reproductive Toxicity.

Group I. Dicamba. The robust summary for a GLP/OECD 2-generation study in rats did not report the size of the observed body and organ weight effects. In the results section, the dose for the F1 females was apparently incorrectly converted from 1500 ppm to 35 mg/kg/day.

Developmental Toxicity.

Group I. Dicamba. The robust summary for a GLP-compliant, EPA guideline developmental toxicity study in rats exposed to technical dicamba by gavage provided most study details, but did not specify the size of the body and organ weight effects or the percentage of high-dose fetuses that showed incomplete ossification of facial and/or parietal bones.

Group III. Sodium acifluorfen. The summary incorrectly stated that the high dose was a NOAEL for fetal toxicity/teratogenicity. The data indicate that the fetal NOAEL was 20 mg/kg/day and the fetal LOAEL was 90 mg/kg/day for significantly reduced pup weight and significantly increased visceral and skeletal abnormalities; resorptions were significantly increased at 180 mg/kg/day.

<u>Ecotoxicity Studies</u>

The IUCLID summaries are discussed separately for each endpoint for each proposed category subgroup.

Group I. IUCLID summaries were submitted for dicamba.

Fish. Missing study details included water hardness, loading, signs of toxicity per concentration, and photoperiod.

Invertebrates. Missing study details included the following: test substance concentrations, number of organisms per concentration, use of proper controls, signs of toxicity per concentration, control response, dissolved oxygen, and whether or not analytical monitoring was performed.

Group III.

Fish. 3-(2-Chloro-4-(trifluoromethyl)phenoxy)benzoic acid in *Pimephales promelas.* Missing study details included test substance purity, and photoperiod. The summary did not indicate whether or not analytical monitoring was performed.

Algae. If available the 72- or 96-hour duration and definitive EC50 values should be provided and clearly stated on the basis of 100% active ingredient (a.i.).

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

References

ECOTOX 2002. US EPA database of ecological toxicity data. http://www.epa.gov/ecotox

EFED 2000. Pesticide ecotoxicity database. US EPA Office of Pesticide Programs Environmental Fate and Effects Division (EFED).

JAPAN 1992. Chemicals Inspection and Testing Institute. Japan Chemical Industry Ecology-Toxicology and Information Center. ISBN 4-89074-101-1 page 3-78. (1992).

US EPA 1998. Status of Pesticides in Registration, Reregistration, and Special Review (Rainbow Report). US EPA/OPP/SRRD. Spring, 1998.

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ECOTOX 2002. US EPA database of ecological toxicity data. http://www.epa.gov/ecotox

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